IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Jaques JOLIVET et al. Examiner: Cybille Delacroix-Muirheid

Serial No.: 10/806,336 Group Art Unit: 1614

Filed: March 23, 2004

Title: METHOD FOR ADMINISTRATION OF TROXACITABINE

BRIEF ON APPEAL UNDER 37 C.F.R. §41.37

MAIL STOP: APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed March 11, 2008, attached herewith is Appellants' Brief on Appeal, pursuant to 37 CFR §41.20(b)(2). This is an appeal from the decision of the Examiner finally rejecting claims 1, 3-15, and 17-60 in the Office Action issued September 11, 2007.

(1) REAL PARTY IN INTEREST

The application is assigned of record to Shire BioChem Inc. (now doing business as Shire Canada Inc.), who is the real party in interest herein. The assignment is recorded in Reel 015664/Frame 0589.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected: 1, 3-15, and 17-60;

Claims allowed: None;

Claims canceled: 2 and 16;

Claims withdrawn: None;

Claims objected to: None;

Claims on Appeal: 1, 3-15, and 17-60. A copy of the claims on appeal is provided in the attached Claim Appendix.

(4) STATUS OF AMENDMENTS AFTER FINAL

No amendments have been filed subsequent to the Final Office Action issued September 11, 2007.

On January 11, 2008, Appellants filed a Reply under 37 CFR §1.116 requesting reconsideration of the rejections. No amendments were presented in this Reply.

Additionally, March 10, 2008, Appellants filed a Petition to Withdraw the Finality of the September 11, 2007 Office Action. This Petition has not yet been acted on.

(5) SUMMARY OF THE CLAIMED SUBJECT MATTER

Appellants' claims include four independent claims, i.e., claims 1, 8, 13, and 47. As set forth in claim1, Appellants' invention is directed to a method for the treatment of cancer within a patient. The method comprises administering to the patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0

μM is achieved during the administration. See, e.g., page 3, line 33 – page 4, line 4, and page 5, lines 7-19. Claim 1 further recites that cancer to be treated is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma. See, e.g., page 11, lines 25-30.

As set forth in claim 8, Appellants' invention is directed to a method for the treatment of cancer within a patient. The method comprises administering to the patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0 μM. See, e.g., page 4, lines 6-10, and page 6, lines 4-14. Claim 8 further recites that cancer to be treated is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma. See, e.g., page 11, lines 25-30.

As set forth in claim 13, Appellants' invention is directed to a method for the treatment of cancer within a patient. The method comprises administering to the patient troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 $mg/m^2/day$. See, e.g., page 7, lines 1-5. Claim 8 further recites that cancer to be treated is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma. See, e.g., page 11, lines 25-30.

As set forth in claim 47, Appellants' invention is directed to a method for the administration of troxacitabine or a pharmaceutically acceptable salt thereof in a host having a tumor. The method comprises administering an amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the amount is sufficient to provide tumor reduction. See, e.g., page 4, lines 12-16, and page 7, line 33 – page 8, line 3.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection on Appeal are:

(1) whether claims 1, 3-15, and 17-60 are unpatentable under on grounds of obviousness-type double patenting in view of claims 1, 2, 3, 9, 10, 14-24, and 30-36 of Gourdeau (US 6,630,480) in combination with Gourdeau (US 6,747,036), Giles et al. (US 6,800,639), Chu et al. (US 5,817,667), and the article by De Bono et al.;

(2) whether claims 1, 3-15, and 17-60 are unpatentable under on grounds of obviousness-type double patenting in view of claims 11-21 of Serial No. 10/824,563 in combination with Gourdeau (US 6,630,480), Gourdeau (US 6,747,036), Giles et al. (US 6,800,639), Chu et al. (US 5,817,667), and the article by De Bono et al.; and

(3) whether claims 1, 3-15, and 17-60 are unpatentable under 35 USC §103(a) in view of the abstract by De Bono et al. in combination with Chu et al. (US 5,817,667) and Benet et al.

(7) APPELLANTS' ARGUMENTS

I. Obviousness-type Double Patenting Rejection in view of Gourdeau (US 6,630,480) in combination with Gourdeau (US 6,747,036), Giles et al. (US 6,800,639), Chu et al. (US 5,817,667), and the article by De Bono et al.

Claims 1, 3-15, and 17-60 are rejected on grounds of obviousness-type double patenting in view of claims 1, 2, 3, 9, 10, 14-24, and 30-36 of Gourdeau (US 6,630,480) in combination with Giles et al. (US 6,800,639), Chu et al. (US 5,817,667), and the article by De Bono et al. This rejection is respectfully traversed.

US '480

US '480 has two independent claims. Independent claim 1 recites a method or treating a patient having chronic myelogenous leukemia or acute myelogenous, wherein the patient has been previously treated with Ara-C. Independent claim 21 recites a method of treating a patient suffering from chronic myelogenous leukemia or acute myelogenous

leukemia, wherein the leukemia is non-responsive to treatment with other chemotherapeutic agents.

None of the claims of US '480 recite administration by continuous infusion, let alone continuous infusion for at least 72 hours. The only description of administration recited in the claims is the administration of effective amounts (claims 1 and 21) and specific amount ranges and dosages (see claims 14-20 and 30-36).

In fact, it is acknowledged in the rejection that the claims of US '480 do not disclose: continuous infusion of troxacitabine; continuous infusion of troxacitabine for a period of at least 72 hours; or achievement of a steady state plasma concentration of troxacitabine of 0.03-2.0 μM. See page 14 of the September 11, 2007 Office Action.

The analysis in an obviousness-type double patenting rejection focuses on the claims (not the disclosure) of the primary reference. Thus, the issue is whether the **claims** of the primary reference, alone or combination with secondary prior art references, establish that the invention claimed in the application is an obvious variant. In other words, in the analysis for obviousness-type double patenting the disclosure of the patent is **not** permitted to be used as prior art. See, e.g., MPEP 804 and *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 23 USPQ2d 1839 (Fed. Cir. 1992).

The rejection as initially presented in the December 19, 2006 rejection relied on the specification of US '480 to support the rejection. However, the present version of the rejection as set forth at pages 13-16 of the September 11, 2007 Office Action does not rely on the specification of US '480. Instead, the rejection merely makes the conclusory assertion that one of ordinary skill in the art "would reasonably conclude that it is necessary for troxacitabine to be administered to a patient via a particular mode, for a particular period of time, which would necessarily achieve a particular steady state plasma concentration."

However, this assertion does not set forth a rationale as to why one skilled in the art would select the administration mode, administration time period, and/or plasma

concentration recited in Appellants' claims. In effect, the rejection asserts that claims of US '480 recite a broad genus of administering troxacitabine by any regime. However, the rejection presents no rationale as to why one of ordinary skill in the art would select, from all possible forms of administering troxacitabine, the specific administration regimes recited in Appellants' claims.

Lokich et al.

Apparently recognizing the deficiency in the rejection, the Examiner refers to Lokich et al. It is noted that Lokich et al. is not listed as a reference relied on in the statement of the rejection (see the bottom of page 13 of the September 17, 2007 Office Action). Lokich et al. was first cited in the Final Office Action and forms the basis for Appellants' Petition to Withdraw Finality.

In any event, Lokich et al. describe the results of a literature survey analyzing the relative dose intensity (DI) and maximum tolerated dose (MTD) for bolus versus infusional administration techniques for 27 anti-neoplastic agents. **It is noted that troxacitabine is not one of the 27 anti-neoplastic agents included in the analysis.**

As shown in Table 6 in the Discussion section at page 22 of Lokich et al., the majority of the agents fell into a category in which MTD and/or DI were relatively comparable for infusion and bolus administration (dose ratio 1 to5). For certain agents (dose ratio ≤ 1), the infusion schedule provided a higher MTD, whereas for other agents (dose ratios 5-10 and 10-20), it was the bolus schedule that provided a "dramatically higher MTD." Further, with respect to the latter group Lokich et al. note that "the antimetabolites are the only drugs represented."

One of the antimetabolite drugs included in the survey was Ara C. This drug was placed in the highest drug ratio column in Table 6, indicating a dramatically higher MTD for bolus administration. It is noted that Ara C is a nucleoside analogue, like troxacitabine. Thus if one of ordinary skill in the art were to expect that anti-neoplastic agents that are nucleoside analogues should be administered in a similar manner, then the disclosure of Lokich et al.

would suggest administration by bolus, not by infusion.

Alternatively or additionally, one of ordinary skill in the art may not have any expectation as to the optimal methodology for administering troxacitabine. Unlike Ara-C and other nucleoside analogues used as anti-neoplastic agents, troxacitabine was the first unnatural L-nucleoside analog to show potent preclinical anti-tumor activity, thus effecting representing a new class of agents.

Overall, the disclosure of Lokich et al. does not suggest the particular mode of administration for troxacitabine recited in Appellants' claims. Combining the disclosure of Lokich et al. with the disclosure of the claims of US '480 would not result in the claimed methods of treatment.

Furthermore, clinical trial results for infusional administration of troxacitabine pointed towards a different infusional administration mode, thus suggesting away from administration of the drug by continuous infusion for a period of at least 72 hours for achieving a steady state plasma or maximum plasma concentration of 0.03 to 2.0 μM. See the page 2, lines 19-34 of Appellants' specification.

Secondary References Gourdeau et al. (US '036) and Giles et al. (US '639)

The first secondary reference, Gourdeau et al. (US '036), is a divisional of the primary reference, Gourdeau et al. (US '480). Gourdeau et al. (US '036) issued on June 8, 2004 (subsequent to the March 23, 2004 filing date of the instant application), from an application filed before the filing date of the instant application. As a result, Gourdeau et al. (US '036) is only prior art, with respect to the instant application, under 35 USC 102(e).

However, in the instant rejection, Gourdeau et al. (US '036) is being utilized to allegedly establish obviousness. With respect to the patent statutes, the conditions for obviousness are set forth in 35 USC 103 (which is titled "Conditions for patentability; non-obvious subject matter"). In section (c) of 35 USC 103 it is stated that:

> Subject matter developed by another person, which **qualifies as prior art only under one or more of subsections (e),** (f), and (g) of section 102 of this

> title, **shall not preclude patentability** under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person. (emphasis added)

The instant application, as well as US '036 and US '480, are commonly assigned. Furthermore, the instant application and both US '036 and US '480 were commonly assigned at the time the invention of the instant application was made. Thus, US '480 is not effective prior art for obviousness determinations under 35 USC 103.

The Examiner cites no authority that suggests that, if US '480 is ineffective prior art for obviousness determinations under 35 USC 103(a), it can still be used as a secondary reference in an obviousness-type double patenting rejection. Moreover, the Examiner's use of Gourdeau et al. (US '036) as a secondary reference is an attempt to circumvent the prohibition against using the disclosure (rather than the claims) of the primary reference in an obviousness-type double patenting rejection. **The Examiner cites no authority which permits the use of the disclosure of a divisional application as prior art when the disclosure of the parent application is unavailable as prior art.**

It is noted that in the Final Office Action, the Examiner appeared to agree that the use of US '036 as a prior art reference was improper. At pages 2-3 of the September 17, 2007 Office Action, the Examiner set forth five points which are asserted to be contentions from Appellants' Reply filed May 14, 2007 (Appellants' do not agree with the implication that these five contentions were the only arguments made in the May 14, 2007 Reply) .

With respect to the first three contentions, the Examiner specifically stated that: "Applicant's arguments identified under items #1-3 are found to be persuasive. The rejections based on said references are withdrawn." See page 4, lines 4-5 of the September 17, 2007 Office Action.

The Examiner characterized contention #3 at the top of page 3 of the Office Action as follows:

"Gourdeau '480 is not effective prior art for obviousness determinations under

35 USC 103(a) because it is a divisional of Gourdeau '036 and both Gourdeau '480 and Gourdeau '036 were commonly assigned at the time of the invention of the instant application was made. Also, Gourdeau '639 is ineffective prior art for the same reason because it was also commonly assigned at the time of the invention of the instant application was made."

Compare Appellants' May 14, 2007 Reply at the top of page 13. It is noted that there is an obvious typographical error in Appellants' arguments, one which is carried over by the Examiner. The paragraph at the top of page 13 of the Reply should have stated that **Gourdeau '036** (rather than Gourdeau '480) was not effective art for obviousness determinations under 35 USC 103(a) and the Examiner presents no authority to suggest that **Gourdeau '036** (rather than Gourdeau '480) can be used as a secondary reference in an obviousness-type double patenting rejection. Also, Gourdeau '639 should instead be Giles et al. (US '639).

In any event, the Examiner agreed that the secondary references in an obviousness-type double patenting rejection Gourdeau et al. (US'036) and Giles et al. (US '639) were not proper prior art references. Since the present rejection also employ Gourdeau et al. (US'036) and Giles et al. (US '639) in exactly that capacity, the rejection should be reversed based on the same arguments that the Examiner has already agreed were persuasive.

In any event, the rejection refers to the description in claims 1 and 4-11 of US '036 of using troxacitabine in combination with doxorubicin and other agents, i.e., a multidrug resistance reversing agent, biological response modifier, and administration of troxacitabine and doxorubicin simultaneously or sequentially. See, e.g., page 15, lines 5-12 of the September 17, 2007 Office Action. It is noted that the claims of US '036 were not published until June 8, 2004. Thus, it is evident that the **claims** of US '036 are not prior art with respect to the instant application. Further, it is noted that such disclosure, if it were prior art, would only be relevant to Appellants' dependent claims 37-46, 52, 53, 56, 57, 59, and 60.

In any event, such disclosure does not suggest treating cancer in a patient by

administering troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours.

The second secondary reference, Giles et al. (US '639), issued on October 5, 2004 (subsequent to the March 23, 2004 filing date of the instant application), from an application filed before the filing date of the instant application. As a result, Giles et al. (US '639) is only prior art, with respect to the instant application, under 35 USC 102(e).

However, in the instant rejection, Giles et al. (US '639) is being utilized to allegedly establish obviousness. Yet, for the same reasons as discussed above with respect to Gourdeau et al. (US '036), Giles et al. (US '639) does not constitute prior art for the reasons set forth in 35 USC 103(c).

Giles et al. (US '639) and the instant application are commonly assigned. Furthermore, the instant application and US '639 were commonly assigned at the time the invention of the instant application was made. Thus, US '639 is not effective prior art for obviousness determinations under 35 USC 103(a). The Examiner cites no authority that suggests that, if US '639 is ineffective prior art for obviousness determinations under 35 USC 103(a), it can still be used as a secondary reference in an obviousness-type double patenting rejection.

The rejection refers to the description in claims 17, 18, and 26 of US '639 of teaching a method of treating pancreatic cancer by administering troxacitabine in combination with gemcitabine, in which troxacitabine is administered in an amount of 1-8 mg/m^2. See, e.g., page 15, lines 13-16 of the September 17, 2007 Office Action. It is noted that the claims of US '639 were not published until October 5, 2004. Thus, it is evident that the **claims** of US '639 are not prior art with respect to the instant application.

In any event, the cited disclosure in Giles et al. (US '639) does not suggest treating cancer in a patient by administering troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours.

With regards to Chu et al. (US '667) it is argued in the rejection that this patent discloses using troxacitabine in the treatment of cancer broadly, and that this encompasses the treatment of, for example, renal cancer. Regardless of this assertion, US '667 does not disclose administering troxacitabine or a pharmaceutically acceptable salt thereof by infusion, let alone continuous infusion, let alone continuous infusion for a period of at least 72 hours.

Finally, the rejection refers to the disclosure of the 2002 abstract by De Bono et al. (see also the discussion of De Bono et al. at page 2 of Appellants' specification). In the rejection, it is argued that the De Bono et al. abstract teaches administering troxacitabine as a daily **30 minute infusion** for five days every 3 to 4 weeks. However, such disclosure does not provide any rationale that would lead one of ordinary skill in the art to select an administration regime in which a patient was administered troxacitabine by **continuous infusion for a period of at least 72 hours.**

In view of the above remarks, it is respectfully submitted that the claims of Gourdeau (US 6,630,480), taken alone or in combination with the disclosures of Gourdeau (US 6,747,036), Giles et al. (US 6,800,639), Chu et al. (US 5,817,667), the article by De Bono et al. and/or Lokich et al., fails to render obvious Appellants' claimed invention. Reversal of the rejection is respectfully requested.

II. Obviousness-type Double Patenting Rejection in view of Serial No. 10/824,563 in combination with Gourdeau (US 6,630,480), Gourdeau (US 6,747,036), Giles et al. (US 6,800,639), Chu et al. (US 5,817,667), and the article by De Bono et al.

Claims 1, 3-15, and 17-60 are rejected on grounds of obviousness-type double patenting in view of claims 11-21 of Serial No. 10/824,563 in combination with Gourdeau (US 6,630,480), Giles et al. (US 6,800,639), Chu et al. (US 5,817,667), and the article by De Bono et al. This rejection is respectfully traversed.

This rejection in view of claims 11-21 of Serial No. 10/824,563, a divisional of

Gourdeau (US 6,630,480), is rendered moot by the abandonment of Serial No. 10/824,563. Reversal of the rejection is respectfully requested.

III. Rejection under 35 USC §103(a)

Claims 1, 3-15, and 17-60 are rejected as allegedly being obvious in view of the abstract by De Bono et al. in combination with Chu et al. (US 5,817,667) and Benet et al. This rejection is respectfully traversed.

The De Bono abstract describes a Phase I study wherein patients were administered troxacitabine "as a 30-minute IV infusion daily for 5 days." In the rejection, it is acknowledged that Appellants' independent claims recite "continuous infusion for a period of at least 72 hours." The Examiner states that this language "could" be construed to mean a continuous infusion over a period of at least 72 hours. See page 19, lines 5-9 of the September 17, 2007 Office Action. Appellants' respectfully submit that the Examiner fails to explain how this language can be construed any other way. The Examiner alleges that this language, "when given its broadest reasonable literal interpretation, encompasses any continuous infusion." This is a conclusory statement. No rationale is presented as to why one of ordinary skill in the art would construe this language in the manner suggested by the Examiner.

The Examiner's argument at page 19 of the September 17, 2007 Office Action regarding half-lives for drug elimination merely refers to an asserted "continuous" amount of drug in the bloodstream. The argument does not provide any reason why one would interpret 30 minutes to be the same as at least 72 hours. The rejection presents no rationale as to why one of ordinary skill in the art would conclude that a 30 minute infusion satisfies a claim limitation of continuous infusion for at least 72 hours.

With regards to the disclosure by Chu et al. (US '667), this disclosure does not mention infusion, or continuous infusion, let alone continuous infusion for at least 72 hours. Thus, US '667 provides no rationale for modifying the disclosure of De Bono in such a manner as to arrive at Appellants' claimed dosage regime. The combined disclosures of De

Bono et al. and US '667 do not lead one of ordinary skill in the art to select an administration regime in accordance with Appellants' claimed invention.

The arguments in the rejection regarding the disclosure of Benet et al. suggest that it is possible to manipulate infusion rate to achieve or maintain certain concentration of a drug. Contrary to the assertions and implications in the rejection, **Benet et al. do not mention the administration by infusion.** Moreover, Benet et al. provide no rationale that would lead one skilled in the art to replace a dosage regime involving daily 30-minute infusions with a continuous infusion for a period of at least 72 hours. The combined disclosures of De Bono et al., US '667, and Benet et al. do not lead one of ordinary skill in the art to select an administration regime in accordance with Appellants' claimed invention.

Apparently recognizing the deficiency in the rejection, the Examiner here also refers to Lokich et al. It is noted that Lokich et al. is not listed as a reference relied on in the statement of the rejection (see paragraph bridging pages 17-18 of the September 17, 2007 Office Action). Lokich et al. was first cited in the Final Office Action and forms the basis for Appellants' Petition to Withdraw Finality.

Lokich et al. describe the results of a literature survey analyzing the relative dose intensity (DI) and maximum tolerated dose (MTD) for bolus versus infusional administration techniques for 27 anti-neoplastic agents. **It is noted that troxacitabine is not one of the 27 anti-neoplastic agents included in the analysis.**

As shown in Table 6 in the Discussion section at page 22 of Lokich et al., the majority of the agents fell into a category in which MTD and/or DI were relatively comparable for infusion and bolus administration (dose ratio 1 to5). For certain agents (dose ratio ≤ 1), the infusion schedule provided a higher MTD, whereas for other agents (dose ratios 5-10 and 10-20), it was the bolus schedule that provided a "dramatically higher MTD." Further, with respect to the latter group Lokich et al. note that "the antimetabolites are the only drugs represented."

One of the antimetabolite drugs included in the survey was Ara C. This drug was placed in the highest drug ratio column in Table 6, indicating a dramatically higher MTD for bolus administration. It is noted that Ara C is a nucleoside analogue, like troxacitabine. Thus if one of ordinary skill in the art were to expect that anti-neoplastic agents that are nucleoside analogues should be administered in a similar manner, then the disclosure of Lokich et al. would suggest administration by bolus, not by infusion.

Alternatively or additionally, one of ordinary skill in the art may not have any expectation as to the optimal methodology for administering troxacitabine. Unlike Ara-C and other nucleoside analogues used as anti-neoplastic agents, troxacitabine was the first unnatural L-nucleoside analog to show potent preclinical anti-tumor activity, thus effecting representing a new class of agents.

Overall, the disclosure of Lokich et al. does not suggest the particular mode of administration for troxacitabine recited in Appellants' claims. Combining the disclosure of Lokich et al. with the disclosure of the claims of US '480 would not result in the claimed methods of treatment.

Furthermore, clinical trial results for infusional administration of troxacitabine pointed towards a different infusional administration mode, thus suggesting away from administration of the drug by continuous infusion for a period of at least 72 hours for achieving a steady state plasma or maximum plasma concentration of 0.03 to 2.0 μM. See the page 2, lines 19-34 of Appellants' specification.

In view of the above remarks, it is respectfully submitted that De Bono et al., taken alone or in combination with US '667 and/or Benet et al. and/or Lokich et al., fails to render obvious Appellants' claimed invention. Reversal of the rejection is respectfully requested.

(8) CONCLUSION

For all of the above reasons, it is urged that the decision of the Examiner finally rejecting claims 1, 3-15, and 17-60, on appeal, is in error and should be reversed.

Respectfully submitted,

/Brion P. Heaney/

_____

Brion P. Heaney
Registration No. 32,542

Filed: July 11, 2008

CLAIMS APPENDIX

1. (Previously Presented): A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0 μM is achieved during the administration,

wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.

2. (Cancelled):

3. (Previously Presented): A method according to claim 1, wherein said cancer is pancreatic cancer.

4. (Previously Presented): A method according to claim 1, wherein said cancer is leukemia selected from acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, and refractory myelodysplastic syndromes.

5. (Original): A method according to claim 4, wherein said cancer is acute myelogenous leukemia.

6. (Previously Presented): A method according to claim 1, wherein a steady state plasma concentration of 0.05 to 0.1 μM is achieved during the administration.

7. (Original): A method according to claim 4, wherein a steady state plasma concentration of 0.1 to 0.42 μM is achieved during the administration.

8. (Previously Presented): A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a

pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0 μM,

wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.

9. (Previously Presented): A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is 0.03 μM to less than 1.0 μM.

10. (Previously Presented): A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is 0.03 μM to less than 0.5 μM.

11. (Previously Presented): A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is 0.03 μM to less than 0.42 μM.

12. (Previously Presented): A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is 0.03 μM to less than 0.1 μM.

13. (Previously Presented): A method for the treatment of cancer within a patient, comprising administering to said patient troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 $mg/m^2/day$,

wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.

14. (Original): A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 1.0 to 11.0 mg/m^2/day.

15. (Original): A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 8.0 to 11.0 mg/m^2/day.

16. (Cancelled):

17. (Previously Presented): A method according to claim 13, wherein said cancer is pancreatic cancer.

18. (Previously Presented): A method according to claim 13, wherein said cancer is leukemia selected from acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, and refractory myelodysplastic syndromes.

19. (Original): A method according to claim 18, wherein said cancer is acute myelogenous leukemia.

20. (Previously Presented): A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 3.0 mg/m^2/day.

21. (Original): A method according to claim 13, wherein said cancer is a solid tumor and the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m^2/day.

22. (Original): A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof 9.5 to 10.5mg/m^2/day.

23. (Previously Presented): A method according to claim 1, wherein said continuous infusion is administered for a period of 3 to 7 days.

24. (Previously Presented): A method according to claim 1, wherein said continuous infusion is administered for a period of 3 days.

25. (Previously Presented): A method according to claim 1, wherein said continuous infusion is administered for a period of 4 days.

26. (Previously Presented): A method according to claim 1, wherein said continuous infusion is administered for a period of 5 days.

27. (Previously Presented): A method according to claim 1, wherein said continuous infusion is administered for a period of 6 days.

28. (Previously Presented): A method according to claim 1, wherein said continuous infusion is administered for a period of 7 days.

29. (Previously Presented): A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m^2/day, said period is 3 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

30. (Previously Presented): A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m^2/day, said period is 4 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

31. (Original) A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m^2/day, said period is 5 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

32. (Original): A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m^2/day, said period is 6 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

33. (Previously Presented): A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 4 weeks.

34. (Previously Presented): A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 3 weeks.

35. (Previously Presented): A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 5 weeks.

36. (Previously Presented): A method according to claim 1, wherein said continuous infusion is by means of continuous intravenous infusion.

37. (Previously Presented): A method according to claim 1, wherein said method further comprises, in combination with said continuous administration of troxacitabine, administering at least one further therapeutic agent selected from nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

38. (Previously Presented): A method according to claim 37, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, imatinib mesylate, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and

Prednisone.

39. (Original): A method according to claim 37, wherein said at least one further therapeutic agent is the multidrug resistance reversing agent PSC 833.

40. (Original): A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from monoclonal antibodies and cytokines.

41. (Previously Presented): A method according to claim 40, wherein said at least one further therapeutic agent is a cytokine selected from interferons, interleukins and colony-stimulating factors.

42. (Original): A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from Rituxan, CMA-676, Interferon-alpha recombinant, Interleukin-2, Interleukin-3, Erythropoetin, Epoetin, G-CSF, GM-CSF, Filgrastim, Sargramostim and Thrombopoietin.

43. (Previously Presented): A method according to claim 37, wherein said troxacitabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially.

44. (Previously Presented): A method according to claim 37, wherein said troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously.

45. (Previously Presented): A method according to claim 44, wherein said troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in separate pharmaceutical formulations.

46. (Previously Presented): A method according to claim 44, wherein said troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations.

47. (Original): A method for the administration of troxacitabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction.

48. (Previously Presented): A method according to claim 8, wherein said cancer is pancreatic cancer.

49. (Previously Presented): A method according to claim 8, wherein said cancer is leukemia selected from acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, and refractory myelodysplastic syndromes.

50. (Previously Presented): A method according to claim 49, wherein said cancer is acute myelogenous leukemia.

51. (Previously Presented): A method according to claim 8, wherein said continuous infusion is by means of continuous intravenous infusion.

52. (Previously Presented): A method according to claim 8, wherein said method further comprises, in combination with said continuous administration of troxacitabine, administering at least one further therapeutic agent selected from nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

53. (Previously Presented): A method according to claim 52, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase,

Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, imatinib mesylate, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

54. (Previously Presented): A method according to claim 13, wherein said cancer is pancreatic cancer.

55. (Previously Presented): A method according to claim 13, wherein said continuous infusion is by means of continuous intravenous infusion.

56. (Previously Presented): A method according to claim 13, wherein said method further comprises, in combination with said continuous administration of troxacitabine, administering at least one further therapeutic agent selected from nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

57. (Previously Presented): A method according to claim 56, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, imatinib mesylate, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

58. (Previously Presented): A method according to claim 47, wherein said continuous infusion is by means of continuous intravenous infusion.

59. (Previously Presented): A method according to claim 47, wherein said method further comprises, in combination with said continuous administration of troxacitabine, administering at least one further therapeutic agent selected from nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

60. (Previously Presented): A method according to claim 59, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, imatinib mesylate, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

EVIDENCE APPENDIX

Not Applicable.

RELATED PROCEEDINGS APPENDIX

Not Applicable.